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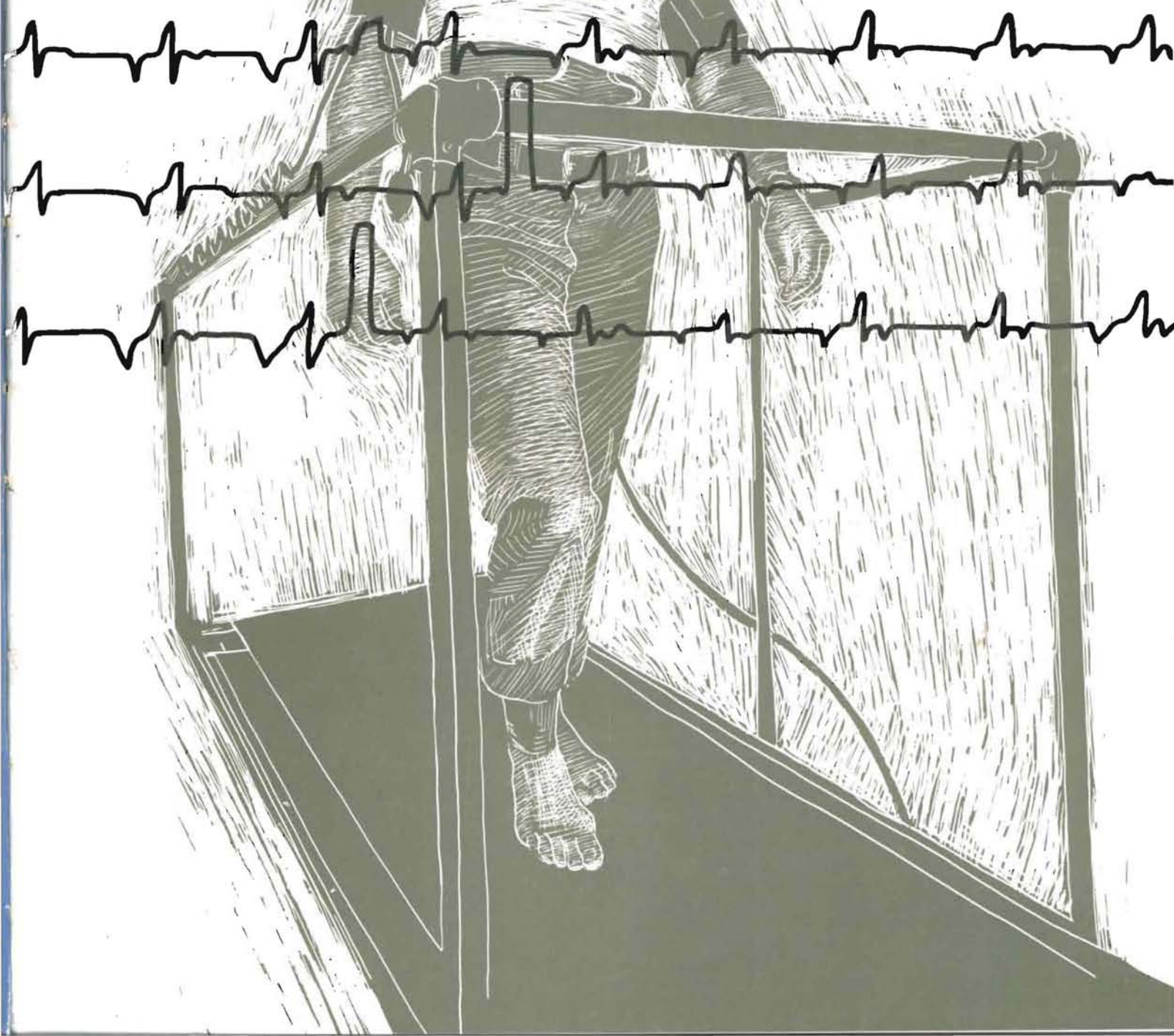
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Washington University School of Medicine

December 1978



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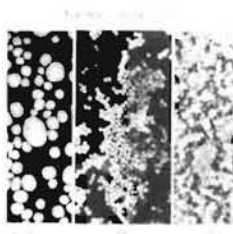
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ON THE COVER:

An artist's rendition of a patient
taking a graded exercise test,
superimposed by an EKG obtained
during the test. This test is part
of the annual physical given to
participants in a major Lipid
Research Center study.

Editor

Sharon Stephens

Staff

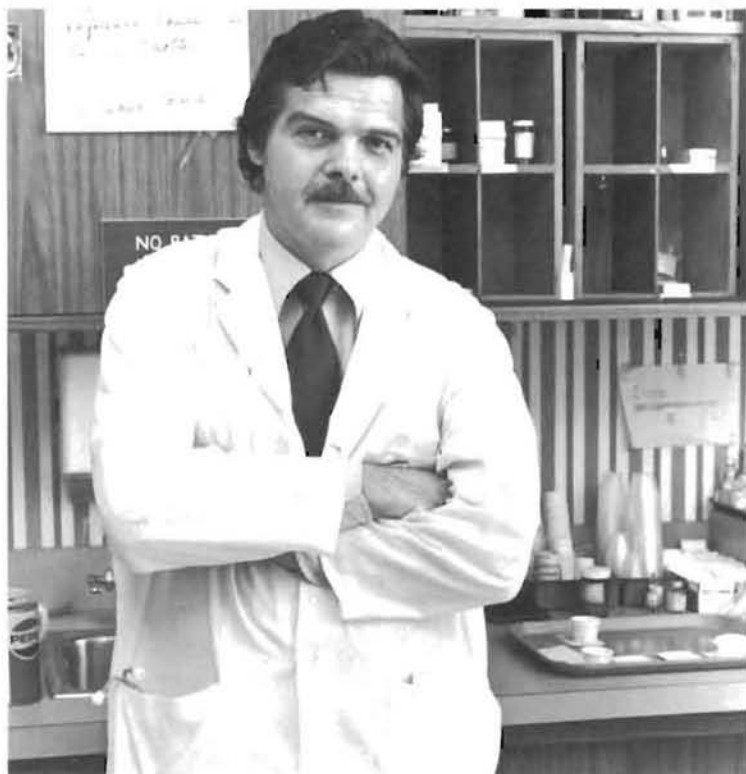
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Clinical Research Center: A different research environment

By Sharon Stephens



Philip E. Cryer, M.D., CRC program director.

To watch Raymond Sander play football with his friends in Seldon, N.Y., you would never guess that less than four years ago he couldn't walk or stand. Victim of a resistant form of rickets, Raymond came to Washington University Medical Center at the age of 12 with bone deformities and in a generally weakened state.

He was admitted to the Clinical Research Center (CRC), where evaluations of his condition were made by Louis Avioli, M.D., head of the Division of Bone and Mineral Diseases, and his staff. A diagnosis was determined and vitamin D and phosphate treatment transformed him into a healthy looking young man with energy to spare.

The Clinical Research Center at Washington University has played a vital role in the evaluation, study and treatment

of patients with various bone diseases. Diabetes Research and Training Center patients also are studied and treated in the CRC and the artificial pancreas was developed utilizing CRC facilities. The Lipid Research Center and the Neuromuscular Disease Center admit patients for research protocols. Eleven departments and 140 investigators are involved in research requiring use of the CRC.

The CRC is a specialized unit for human research and top-notch patient care. Established in 1960, the Washington University CRC is one of the oldest and one of the largest (with 25 adult and 8 pediatric beds), as well as one of the most scientifically productive in the country. It is supported by a grant from the Division of Research Resources of the National Institutes of Health.

Located on the fourth and fifth floors of Barnard Free Skin and Cancer Hospital and the seventh floor of St. Louis Children's Hospital, the CRC floors resemble a typical hospital. But there is little typical about the staff, patients or the day-to-day routine in this mini-hospital within a hospital.

This uniqueness is necessary for the kind of research which is done in the CRC. "Systematic, controlled clinical research can't be done in a normal hospital setting," explains Philip Cryer, M.D., director of the CRC and associate professor of the Department of Medicine.

In addition to patient beds, the CRC has seminar areas, food preparation areas, specimen collecting facilities and a central laboratory.

"Probably the most significant difference between the CRC and the normal hospital setting is the specially trained nurses and dietitians. These people are experienced in protocol research and are an important link in the success of the studies," Cryer says.

Darryl DeVivo, M.D., associate director for the Children's Unit of the CRC, professor of the Department of Neurology and Neurological Surgery and professor of the Department of Pediatrics agrees. "I think the nursing personnel are really the backbone of the day-to-day activity and they deserve a tremendous amount of credit for their interest and enthusiasm and attention to detail," DeVivo says.

"That applies to the dietary personnel as well. They are very instrumental in many of the protocols that require a full understanding of exactly what the patient is eating. We are fortunate to have such outstanding personnel in these areas."

The nurse/patient ratio in the CRC is higher than a regular hospital floor. CRC research calls for 24-hour urine collections, timed blood samples and intricate diagnostic procedures which require a large staff.

"For instance," DeVivo says, "if a child has to fast as part of a protocol, it is very risky to do that on a ward where you might not be able to have close minute-to-minute supervision of the young infant or child. I think for the patient's safety, and also for the quality of work being done, that these types of diagnostic and research oriented procedures should be done on a research unit."

Jane Hamilton, R.N., nursing administrator, has been at the CRC for 15 years. "I wouldn't think of going back to regular nursing," she says. "In the CRC, nurses really have to use their own judgment. It's a constant learning experience, not only to keep up with the profession but with the research protocols as well. Just when you think you know a certain protocol and have learned what to expect, it changes."

Hamilton, who describes herself as a player-coach, says the nursing staff has tried to break down the traditional formalities between staff and patients. "We want our patients to feel free to talk with us and we keep nothing from the patient. It's their disease and they have a right to be informed and understand it."

Concise diets must often be planned for CRC participants in order for them to adhere to research protocols. Dietitians, therefore, play an important role in the CRC. Norma Janes, supervises the activities of the dietitians and nutritionists on staff and has been with the CRC since its inception in 1960.

"The studies in the CRC often require special diets and a record of exactly what the

patient is getting in liquid and solid food. Some studies require that food be weighed to one-tenth of a gram. In other studies certain elements of the food such as carbohydrate or mineral content, must be measured. To do this two servings of each meal are prepared for the patient. One is served to the patient and the other is blenderized and sent to the laboratory for analysis. In these studies the patient must leave nothing uneaten.

About 80 per cent of CRC patients are receiving special diets prepared or modified in the Center's metabolic kitchen.

"We buy all the food for some studies at the same time before the study begins," explains Janes. "This can be quite a job since some of the protocols may last one or two months. However, it is necessary so we can get the same lot number for all the food will be used. Then we store the food in portion sizes."

"We interview the patients and try to build their diet around foods they can tolerate. One or two months is quite a length of time for a patient to be confined to a hospital. We try to make meals as pleasant as possible and still follow the protocol."

"The work done in the CRC requires a great deal of teamwork," Janes says. "The dietitians work with the researcher to achieve research goals."

Many research goals have been met since the CRC at Washington University was established. Much of the credit is given to David M. Kipnis, M.D., Busch Professor of Medicine and Chairman of the Department of Medicine, who was the Director of the CRC from its inception in 1960.



"Dr. Kipnis has been a skilled administrator as well as a highly productive investigator. The growth and success of the CRC have been no small reflection of his efforts," says Cryer.

"We are proud of our unit," adds DeVivo, "and that pride is predicated on the productivity of the unit over the years under the strong leadership of Dr. Kipnis and Dr. Cryer and the rest of us who from day-to-day try to make it a first-class place for doing the kind of work it was designed to do."

Often, work done in the CRC has an enormous effect on the quality of life of patients, like Raymond Sander. This was also true in the case of Amy Windeknecht. Amy was less than a year old when she was referred to the Medical Center from rural Missouri after having had two severe attacks of lactic acidosis accompanied by hypoglycemia.

There were several people involved in research of metabolism-related diseases and they began an investigation into Amy's condition. The investigators soon suspected that Amy had an enzyme defect and began searching for the specific problem. Eventually it was found that Amy lacked the vital enzyme Fructose-1-6-diphosphatase. This is one of the enzymes required to convert lactic acid into glucose.

If this enzyme is missing, too little glucose is produced resulting in low blood sugar or hypoglycemia and lactic acid accumulates causing lactic acidosis.

Once Amy's trouble was recognized, the doctors enlisted the help of the CRC dietitians to formulate a diet which would satisfy her requirements for normal growth

Darryl C. DeVivo, M.D., associate director of the children's CRC.

and development, be palatable and, at the same time, devoid of those foods which could conceivably cause her problems.

Had the abnormality not been discovered, Amy could have suffered brain damage and possibly death.

Since this enzyme deficiency has been identified other such cases have turned up with increasing frequency. In addition, diagnosis was made easier. During Amy's stay in the CRC, new types of infusion tests and analytical techniques were developed which made it possible to detect and identify specific defects by injecting different kinds of materials intravenously and measuring the effects on blood sugar and other chemical substances.

These methods and others developed have proven

useful as the CRC is very involved in the study and treatment of all types of metabolic and endocrinologic diseases ranging from enzyme deficiencies to diabetes to ketotic hypoglycemia. This is the largest area of research interest accounting for about one-third of CRC activity.

Both Raymond Sander and Amy Windeknecht are dramatic examples of the good to come from CRCs. But this good would be financially impossible for patients without the grant support of the CRC from the Division of Research Resources of the National Institutes of Health.

The national CRC program has fostered many innovations and medical advances, but much of the research work in many major areas continues to be an unending process.

"Progress goes piece by piece, particularly in this day and age," says Cryer. "You take an idea and you ask a question. You may answer that question the way you expect to or answer it completely differently, and that raises additional questions.

"Everyone's work, particularly when you do clinical research, is based on a large body of other people's work," he says. Because the CRC is multi-disciplinary, people with different areas of expertise can help each other.

"It makes for an exciting environment with new questions being raised and different disciplines interacting. The net effect is that we can be a major participant in the development of new knowledge concerning human disease."

The Clinical Research Center was established to shorten the lag time between

the development of new basic information and its application to the diagnosis and treatment of patients.

Aware of research projects appropriate to their patients, physicians may suggest participation. With voluntary, informed consent, the patient becomes the key link.

"Patients are very important to us, not only from a research viewpoint, but from a caring position, as well," Cryer says. The Medical School and the CRC staff are very concerned about the patient's protection. Any study that is done in the CRC must be approved by the Washington University Human Studies Committee and by the CRC Advisory Committee.

"The need and reasons for each protocol and the scientific merit and procedures are examined," Cryer says. The

Human Studies Committee approval is for a maximum of 12 months and they also have interval surveillance during which they investigate the progress of the study and any unexpected changes or complications.

"Our work is tightly supervised and no studies are done until the patient understands and signs the consent form," Cryer says.

Once patients are recruited for a study, the work begins and may continue for months or for years. The number of patients involved in any one study varies, but the number of patients involved in the CRC has increased progressively since 1960 reaching a level of more than 1,200 in-patients a year. An additional 1,800 people participate in studies on an out-patient basis.

The person responsible for keeping track of the many patients and studies is Claudia Long, administrative coordinator of the CRC. She handles the administrative activities and details of the Center. "Our CRC staff is great," Long says. "They're the best in their fields. They care about their research but they care about the patients too."

"One of the great things about the Center is its home-like atmosphere. Patients and staff become family here very quickly. In fact, sometimes patients are reluctant to leave."

Recently 100 obese patients underwent iliojejunal bypass surgery. This involved bypassing part of the small intestine. "There are many series which are larger than this one," explains Cryer. "The unique thing about this one was that the patients were studied



Joyce Kuntze, head nurse, children's CRC.

after they had the operations as well as before. The follow-up was not just intensive, it was 100 per cent. John Halverson, M.D., assistant professor of surgery, who completed this study begun by Dr. Leslie Wise, knows what happened to every patient, which is unusual in most surgical studies."

The data was accumulated, computer stored and analyzed. This process revealed that the operation was extraordinarily dangerous. "Other more superficial reports were generally positive about the operation," Cryer says.

This study, however, followed the patients to find that five out of the 100 died. Another 20 per cent had to have the operation reversed because of a variety of complications. So we are talking about one out of four absolute failures.

"About half of the remaining people are having chronic problems," Cryer says. "Only a fourth of those undergoing the operation have lost and kept off weight and feel well and healthy."

CRC physicians are now conducting a similar study to examine the effectiveness and safety of gastric bypass surgery for obese patients.

"This operation decreases the volume of the stomach so a person becomes satiated earlier. Theoretically this should have less serious problems. But we will have to see."

Another study involving obese patients is one looking at the impact of obesity in developing adult onset diabetes and high blood lipids.

Investigator Andrew Goldberg, M.D., assistant professor of medicine, explains that middle aged women often develop diabetes and later on have vascular disease in their



50s, reducing their longevity by ten to 15 years.

"The end-point in this study," explains Goldberg, "is to find out how to reduce the risk factors for cardiovascular diseases. Obesity causes a lot of things which lead to cardiovascular disease."

Patients in Goldberg's study are admitted to the CRC initially for up to four weeks. They are put on diets which are planned to keep them at the exact same weight while a variety of studies are done. Then a program of weight reduction is begun.

"With the help of a dietitian and social worker we try to behaviorally modify the patient's eating habits," Goldberg

says. "So far it appears that patients who successfully lose weight seem to show improvement in glucose tolerance and blood lipids."

"We have been able to withdraw insulin and medication for high blood pressure for a number of patients."

Diabetes has been a major area of research in the CRC in part due to the existence of the Diabetes Research and Training Center under the direction of William H. Daughday, M.D.

Diabetes research and studies in many other areas have depended on the assistance of the CRC core laboratory.

"The core laboratory provides both a research func-

tion and a developmental function," explains Cryer. "Measurements of a variety of hormones and metabolic substrates, intermediates and products are performed in the core laboratory on samples from CRC patients."

"These determinations," he says, "are not available through the routine chemistry laboratories of the hospital. In addition, a variety of analytical techniques have been originated or developed in the core laboratory."

Radioimmunoassays for cyclic nucleotides in tissues and biologic fluids were first developed at Washington University School of Medicine. Fluorimetric techniques for the



Mary Bahan, R.N., Virginia Bischof, R.N., assistant nursing administrator, George Featherson, LPN, and Deborah Ratliff, R.N. in the CRC.



CRC dietary aide Sarah Stanfield (left) instructs Anne Rejent, Barnes dietetic intern, on the importance of exact measurements.

measurement of metabolic intermediates have been micro-adapted for application to small quantities of tissue or plasma.

"A major analytical advance has been the application of gas chromatography and mass spectroscopy to the measurement of stable isotopes of glucose and alanine," says Cryer. "This development permits dynamic measurement of the formation and utilization of glucose, a primary metabolic fuel, and that of alanine, a major

glucose precursor, in CRC patients."

The research done in the CRC has covered an incredible number of health problems and disease processes.

Studies on depression, hypertension, cancer chemotherapy, skin problems and muscle function illustrate the diversity of interest.

One study investigated reasons for infertility in women who had lost their periods and had a breast discharge. It was found that a common cause of infertility was pituitary tumors detected because of elevated prolactin

levels being secreted by the tumor. The first immunoassay for prolactin was developed during this study at Washington University School of Medicine and is now done all over the world.

The end result of the study was that a common cause of infertility could be resolved by removing the pituitary tumor causing it.

There also are many studies ongoing in the Children's Unit of the CRC. Many of them involve enzymatic defects as in the case of Amy Windeknecht.

A number of studies of neurological and neuromuscular diseases also are done. One long range research is being done with epileptic children. "We

have been studying the use of ketogenic diet for the treatment of intractable epilepsy," explains DeVivo. "Although this form of treatment was introduced in the 1920s, its use waned when more effective anticonvulsive drugs were introduced.

"During the last five to ten years there has been renewed interest in the ketogenic diet, mainly because it continues to work in certain patients who have been resistant to all the drugs that we have available.

"We have studied about 75 children and out of that population maybe 60 per cent of them have been totally controlled on the diet together with use of drugs. In certain instances some of these children were having 50 to 100 seizures a day prior to using the diet. Our dietitian/nutritionist runs the pediatric metabolic kitchen and is responsible for instructing parents how to continue the diet once they go home," DeVivo says.

Another area of research with children has been growth studies under the direction of Virginia Weldon, M.D., associate professor of pediatrics. William Daughaday, M.D., pioneered at Washington University School of Medicine in the treatment of children with growth problems since the early 1960s.

Many of these children are deficient in growth hormone made by the pituitary gland. Children now come from all over the world for diagnosis and treatment. "There are a variety of reasons why these children may be short of stature," DeVivo says. "We are trying to find these causes and treat them if possible." Significant work has been done with injecting growth hormone, but while successful, this is a limited avenue of treatment since it takes extractions from more than 100 human pituitary glands to treat one patient for one year and treatment may take 10 years.

Some studies such as those testing the efficacy of cancer chemotherapy methods transcend the boundaries of the pediatric and adult CRC. Likewise, the many researchers working in the CRC overlap in their areas of interest. "The rich collaborative activity that goes on has always been one of the virtues of research at Washington University," says DeVivo.



Jane Hamilton, R.N., nursing administrator in the CRC.

The Clinical Research Center is an excellent example of collaboration. Pathologists, pediatricians, surgeons, ophthalmologists, basic scientists, psychiatrists and neurologists and medical researchers of all areas of expertise work together to advance their common knowledge.

Thus, the CRC, though it does not directly support basic research, provides the critical opportunity to carry the advances of such research to

the bedside in a controlled, supervised manner.

The availability of a Clinical Research Center at Washington University School of Medicine, as well as at other institutions, has made a dramatic difference in the lives of people like Randy Sanders and Amy Windeknecht. But CRC research also plays an equally important, although a less visible, role in solving of medical mysteries which when added together make significant contributions to the care of large numbers of patients.

A Search For Sexual Identity

"The omnipresent process of sex, as it is woven into the whole texture of our man's or woman's body, is the pattern of all the process of our life."

Havelock Ellis

by Katherine S. Robbins

Monica Abbott Jamison is 23 years old. She is an attractively dressed female, who is successfully employed as a hairdresser. Described by her friends and employers as a cooperative and pleasant personality, Monica has a record of reliability. She is a thoughtful, articulate and insightful conversationalist whose judgment and cognitive functions are perfectly normal.

However, what separates Monica from normal females is the fact that she was born a biological male—christened Charles Abbott Jamison. She was diagnosed at Washington University School of Medicine as having gender identity dysphoria, and has successfully undergone sex reassignment surgery.

Washington University School of Medicine is currently involved in a clinical research project for transsexuals under the direction of Paul M. Packman, M.D., associate professor of psychiatry, with the assistance of James G. Bucy, M.D., assistant clinical professor of genitourinary surgery, and Robert C. Wray, Jr., M.D., associate professor of plastic and reconstructive surgery.

At this stage, gender identity dysphoria is considered a psychiatric illness because the manifestations are behavioral and the cause is unknown. The primary role in patient care is assumed by the psychiatrist who establishes the diagnosis and makes the appropriate referrals for hormone therapy, surgery and legal advice.

By definition according to Webster's Dictionary a transsexual, unlike a homosexual or

a transvestite, is a person genetically of one sex with a psychological urge to belong to the opposite sex. This desire may be carried to the point of undergoing surgery to modify the sex organs to mimic the opposite sex.

Transsexualism and transvestism have been known under various names in many cultures and in all parts of the world. The ubiquity of these conditions suggests that they may represent, not a corrupt manifestation of a culture, but rather the survival of an ancient and natural tendency of primitive men.

Herodotus described the phenomena as mysterious Skythian illnesses from the northern shores of the Black Sea. There, apparently normal males would dress in feminine clothing, do the work of women, and generally affect feminine character and behavior.

The presence of transsexuals and transvestites in classical Greece is suggested by a picture of Hercules dressed in feminine clothes, serving his mistress Omphale. They were also present in ancient Rome, particularly at the time of the decline. At the beginning of modern times, the most notorious were three Frenchmen, the brother of King Henri III, the Abbé de Choisy, and the proverbial Chevalier d'Eon, whose name gave rise to the term eonism, a synonym for transvestism.

Since the case of Christine Jorgensen in 1953, transsexuality has become more widely recognized. Christian Hamburger, M.D., and his collaborators in Denmark evaluated George Jorgensen and decided to treat him with not only hormones, but with surgical

procedures, as well, in order to convert George into Christine. At that time transsexuals were referred to as eonists (transvestites), people who cross dressed.

According to Hamburger eonists were persons with a fundamental feeling of being victims of a cruel mistake—a consequence of the female personality in a male body. They experienced an extremely pronounced desire to wear women's clothes. This, however, was understood as only one of the many means through which the person attempted to identify himself with the female sex, to be regarded as a woman by society, and to be called by a woman's name.

"Men's clothes are felt to be an intolerable disguise and manly occupations a severe burden," Hamburger said. "The person conceives it to be against his nature to have to live and act as a man, with never the possibility of being able to follow the spontaneous inclinations of his own self." According to Hamburger this entailed continual mental stress that led to more or less intense neurotic conflicts and possibly to suicidal attempts. When male transvestites, known as transsexuals today, wore feminine women, they experienced mental relaxation, balance and inspiration, and the enjoyment of life.

"The wearing of women's clothes in these cases does not aim at, and does not involve, any sexual satisfaction, and it is a characteristic feature that the dress is respectable and in no way provocative," Hamburger continued. "On the whole, the

sexual life generally plays but a minor part. Attraction to normal, heterosexual men is no infrequent phenomena, but the genuine transvestite is disgusted by relationships with homosexual men. Attraction toward the female sex is generally on a higher plane, but only rarely, and possibly never, is such attraction of a direct erotic nature," Hamburger said.

In the search for a cause for transsexualism it is helpful to define sex and its anatomical differences. Instead of the conventional two sexes there may be up to ten or more separate concepts and manifestations of sex and each could be of vital importance to the individual. Some of them are: chromosomal, genetic, anatomical, legal, gonadal, germinal, endocrinological (hormonal), psychological and the social sex, usually based on the sex of rearing.

The chromosomal sex, equated with the genetic sex, is the fundamental one as it determines gender. The normal male chromosomal constellation is XY; the normal female is XX. Various genetic abnormalities such as Klinefelter's syndrome (XXY), when 47 chromosomes exist instead of the normal 46 have been noted to exist in individuals with atypical gender identity behavior. These "mosaics" of sex, depending on their severity, could be responsible for testicular cell distortion, and genital as well as skeletal disorders.

There are, however, several disorders that are genetic and

are related to X,Y chromosomes or to metabolic deficiencies. An individual with Turner's syndrome, characterized by one instead of two X chromosomes, has no estrogens and her body type is that of an infantile female in that there is no breast development, and no onset of menarche. Individuals with testicular feminization, a target organ androgen receptor disorder, are often not diagnosed until puberty when the growth of breasts occurs, but no pubic hair or onset of menarche.

Phenotypically they appear to be female and usually have been raised as females, so they do not present with gender identity confusion even though they are genetically X, Y and have normal circulating levels of androgen. Individuals with virilizing adrenal-genital syndrome have enzyme absence in adrenal tissue which converts progesterone and its metabolic products into adrenal corticoids. They usually do not have gender identity dysphoria which indicates that no hormonal abnormality can account for the development of a masculine or feminine gender identity.

However, they have many masculine personality traits. They are known as tomboys, have strong athletic interests and enjoy competitive games. They do not like dresses, and, as children, they prefer to play with guns, cars and trucks instead of dolls.

The normal female or male will reveal their sex through the presence or absence of primary and secondary sex characteristics known as anatomical sex. Reproductive organs are considered primary sex characteristics, while for males, a deep voice, chest and facial hair, and for the females, breasts, and a wide pelvis are considered secondary sex characteristics. In the case of a developmental anomaly during gestation, an hermaphroditic deformity is



possible when both male and female reproductive organs are present. An hermaphrodite has the gonads of both sexes independent of what its body looks like.

The visible sex organs provide the most direct method of differentiation. This method, employed in everyday practice, is known as the legal sex, though it is not actually defined in legal codes. However, due to incompletely developed organs causing pseudohermaphroditic deformities, the obstetrician may be deceived. Pseudohermaphrodites have the gonads of their biological sex, but the opposite phenotype (visible properties).

The gonads, which include the ovaries and testes, are the primary sex glands. They produce the germ cells which determine the germinal sex

because they produce either sperm or ova (eggs).

The amount of androgens, the male sex hormones, and estrogens, the female sex hormones, stimulate the development of secondary sex characteristics. Androgens and estrogens are present in both males and females in varying degrees. Testes as well as the male adrenals produce small amounts of estrogens. Androgens can be found in the ovaries and in the adrenals of females. The diverse amount of sex hormones in both sexes can have an influence on appearance as well as behavior. Treatment with hormones during pregnancy can make distinct impressions on the anatomical sex feminizing a male and masculinizing a female. None of the various concepts of sex is fixed or unchangeable except the genetic sex.

The psychological sex is that which an individual believes

Paul M. Packman, M.D. associate professor of psychiatry

that he is. This gender identity is the sum total of a conditioning process (imposed on a biological substrate) and includes how one is raised, how society views him, how one's family responds to him and is usually quite fixed by age three to five. For example, an abnormal situation would be a biological male raised as a female.

Social sex could be described as that in which an individual dresses and finds his place in society. Usually, the psychological sex, social sex and the sex of rearing in childhood blend with the various other definitions of sex.

Although the cause or causes of transsexuality are unknown, Packman believes the



James G. Bucy, M.D., assistant clinical professor of genitourinary surgery

condition is biologically determined. "In the past three years we have evaluated about 75 patients and I don't think any two of them have had the same kind of upbringing, background or family circumstances," he says.

"Their problem is gender identity, but not because of how they were reared," Packman continues. "Some are from broken homes, some from stable homes; some from families where all of their siblings are of the opposite sex, some where they are all of the same sex. They are black, white, and from every socioeconomic level. Some have strong fathers, and some have weak fathers; some have strong mothers, and some have weak mothers. We don't observe any consistency in their background. However, if

they are transsexual, then they all exhibit the same symptoms."

On the research end of the project Packman is using an androgen sterilized rat to measure hypothalamic metabolism. This model, originally described by C. Barraclough, M.D., Univ. of Maryland and R. Gorski, M.D., U.C.L.A., involves giving a very small dose of testosterone to a newborn female rat. When it grows up it is sterile—it does not ovulate because it does not have the estrous cycles equivalent to ovulatory cycles in humans. Moreover, the androgenized female demonstrates masculine sexual behavior.

"In open field behavior, male rats will cross fewer grids than a female. The androgen sterilized females cross grids at approximately the same rate as the males. Female rats prefer sweet water; male rats don't show a preference, and the androgen sterilized females

don't either. Their entire behavior is affected because of the testosterone treatment," Packman says.

The female rat must be treated within five or six days of life. If they are given testosterone at day ten they will grow up as a normal female rat. "There is a critical period of sexual differentiation occurring in the brain of rats at that age," Packman explains. "Something is irreversibly programmed, but the mechanism for how it works is not clear."

Studies have shown that what seems to be happening is that the testosterone is being converted to an estrogen type compound. High doses of estrogen can induce the same thing. "The fact is that early hormonal exposure results in abnormal sexual behavior in the female rat," Packman says.

This discovery in the behavior of rats is what attracted

Packman to the patient problem. "In rats I have found that long term persistent metabolic changes in certain hypothalamic nuclei are present even into adulthood," he says. In addition to these brain biochemical changes, Packman is looking at other features in these animals. "We want to compile more detailed studies of rat hormone level fluctuation and measure pituitary responsiveness," Packman says. From a clinical standpoint, Packman is looking at hormone levels in humans.

The first step in the diagnostic treatment process of a transsexual is the psychiatric interview. "What we do is evaluate patients who have approached us directly or been referred for sex reassignment surgery. We use the Renard research criteria for psychiatric illnesses, take a detailed history of the patient's emotional developmental history and sexual history. In this way we arrive at a diagnosis of gender identity dysphoria and are able to exclude other psychiatric problems," Packman says.

Both Packman and Jack Croughan, M.D., assistant professor of psychiatry, generally see patients several times during the process of evaluation over a period of several months. "We see the patients independently of each other to provide two independent evaluations in order to arrive at a diagnosis. Then we get together and discuss our findings," Packman says.

If a diagnosis of transsexualism is made, the patient is referred to an endocrinologist who starts them on hormone therapy. Then after being on hormones for a period of at least one year, living, operating, and functioning in the sex that they wish to be, they are re-

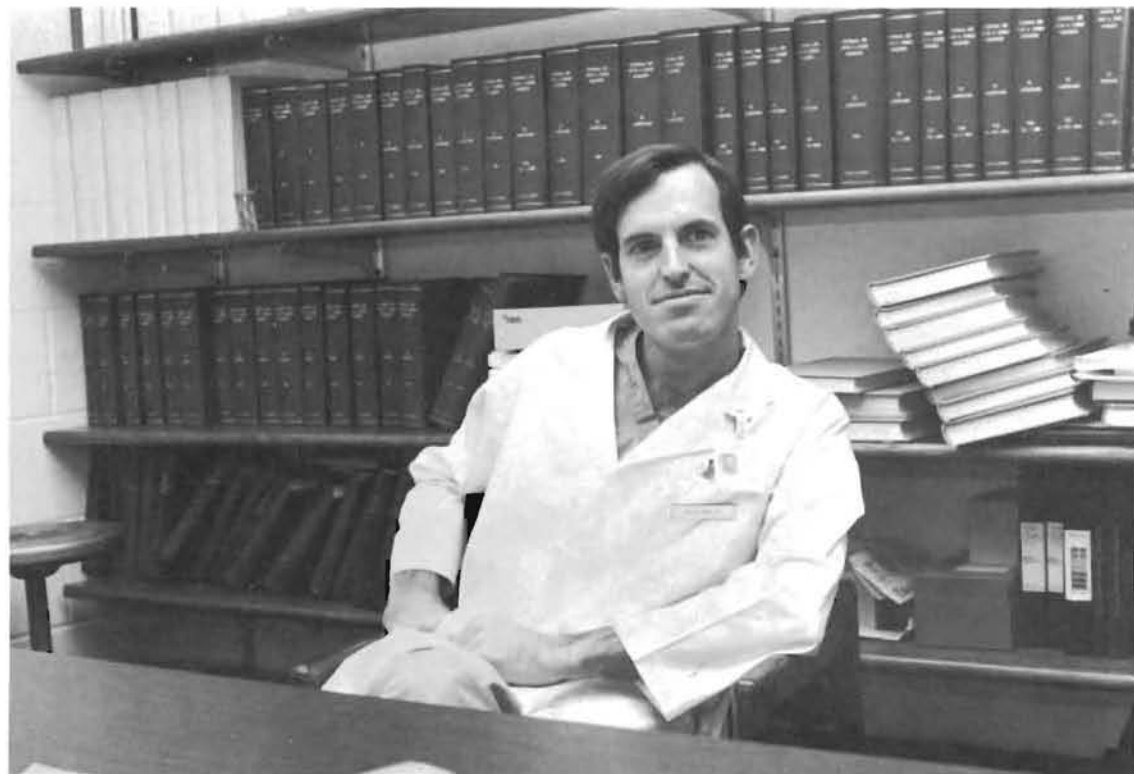
Robert C. Wray, Jr., M.D., associate professor of plastic and reconstructive surgery

ferred to Bucy and Wray for sex reassignment surgery.

The patient's first encounter in the diagnostic process consists of general fact finding. "The questions refer to medical history and hospitalizations, where they live, education and employment history," Packman says. "We want an overview of their socioeconomic and educational level. One of the things we intend to analyze is whether or not transsexuals have difficulty making a living because of gender identity problems. The trend for transsexuals who have had surgery is an increased ability to cope."

Charles Abbott Jamison's medical history reveals no operations, hospitalizations, or any major medical illnesses for which treatment was required. Charles was born in Kansas City, Mo., and has completed approximately 60 hours of college credit at Penn Valley Junior College. His employment record while dressing and acting as a female includes working as a secretary, and modeling make-up products for a prestigious cosmetic company.

The psychiatric interview follows, which—if the ultimate diagnosis is gender identity dysphoria—will rule out depression, drug abuse, schizophrenia, alcoholism, homosexuality, transvestism and antisocial behavior. "Many transsexuals have depressive episodes known as secondary depression which they relate to the difficulties they're experiencing because of their gender identity problems," Packman says.



Charles Abbott Jamison's psychiatric history reveals depressive symptoms, including low mood, irritability, feelings of guilt, initial and terminal insomnia, decreased libido, and loss of interest in people and life in general. He relates these depressive symptoms to his gender identity problems. There is no other history of psychiatric illness within his immediate or extended family.

Upon completion of the psychiatric illnesses interview, Packman takes a detailed history of the patient's emotional developmental history. "We deal with the problems of who they grew up with, whether or not they lived with their parents, what kind of interaction they had with their parents, and what kind of play activity they engaged in. Males, for whatever reason, prefer guns, trucks and so on,

while male transsexuals don't generally select those kinds of toys," Packman explains.

Charles Abbott Jamison's social history indicates that as a child he took a feminine role in social games such as house, and avoided playing cowboys and Indians, cops and robbers, and war. He preferred to play with dolls, and tea sets over guns, trucks, cars and toy soldiers. He disliked such vigorous and competitive sports as basketball and football which involved a great deal of physical effort.

One of the more striking features of transsexualism is the early onset of symptoms—usually appearing by age eight. Transsexuals continually verbalize their desire to be a member of the opposite sex throughout their psychosexual development, even before they are old

enough to have knowledge about sexuality.

Some of the more prevalent psychological features of a male transsexual include cross dressing, dressing in clothing intended for the opposite sex, preference for the feminine role, feeling of belonging to the female sex and desire for (adoptive) motherhood.

Their preference for the feminine role includes dressing as a female, conducting social activities in a feminine role, and having a feminine occupational or professional outlook. Almost all transsexuals say that they are a female, trapped through some bizarre biological error, in a male body.

They express a strong preference for motherhood and many of them are disappointed by the fact that they are unable to bear children after their

phenotype has been surgically changed. Many of them see themselves as subsequently marrying and raising a family by adopting children.

Charles Abbott Jamison felt early on in life that he was a mistake of nature. He had rather intense feelings that he should have been a female. By age eight he knew that he felt different from other males—that he behaved, thought, and was more comfortable as a female. He played feminine roles in games, and fantasized being super woman. His history of cross dressing dates back to age six. He became very interested in clothing, liked it, and paid attention to it. He often wore his sister's dresses and jewelry, and thought that he looked rather well-dressed.

Packman takes a sexual history of the patient in order to determine whether or not they exhibit the sexual features of male transsexuality. At the time of puberty, patients report a disgust with the development of their primary and secondary sexual characteristics. This disgust may be so great that they develop an abhorrence of their own genitalia and would like to be rid of them. Body congruence and self image are often more important to the transsexual than an active sexual life.

Transsexuals prefer sexual relationships with normal heterosexuals and do not consider this homosexual behavior. They do not consider themselves homosexuals. In fact, sexual relationships with members of the opposite biological sex are considered to be homosexual.

Charles Abbott Jamison has had two long term romantic relationships with heterosexual males. He dated them for several months before they discovered that he was in fact a male. After recovering from the initial shock these individuals maintained a satisfactory romantic relationship for quite some time.

"It is important to distinguish among male transsexuals, transvestites and homosexuals," Packman says. "No confusion about gender identity exists in transvestites or homosexuals. They do not think they are members of the opposite sex, do not wish to live as members of the opposite sex, and do not live their sexual life as members of the opposite sex. Homosexuals and transvestites are not interested in hormone therapy or surgical conversion."

While both transvestites and transsexuals cross dress, the frequency of cross dressing in transvestites is lower. Because cross dressing is more in keeping with a transsexual's gender identity.

The transsexual is unhappy as a member of the sex (or gender) to which he was born. They are physically normal, yet feel that they belong to the opposite sex. They want to be and function as such, not merely appear so. They can appease themselves temporarily by cross dressing, but that is only incidental.

Charles Abbott Jamison meets all of the criteria to establish a diagnosis of gender identity dysphoria. He felt an aversion to competitive games, and rough outdoor activity at a young age and had a lifelong preference for the feminine role. He had an early desire to be female before knowing about sexuality, and has a history of cross dressing. The patient has noted disgust with the development of his primary and secondary characteristics. He has been referred to an endocrinologist for hormone therapy.

If a diagnosis of gender identity dysphoria is established, the patient is referred to an

endocrinologist and started on hormone therapy. While the minimum time period required for the therapy is one year prior to surgery it is often extended to 18 months or two years. The treatment consists of administration of estrogens to male transsexuals and androgens to female transsexuals. Male transsexuals usually begin electrolysis simultaneously with the hormone therapy in order to permanently remove facial hair.

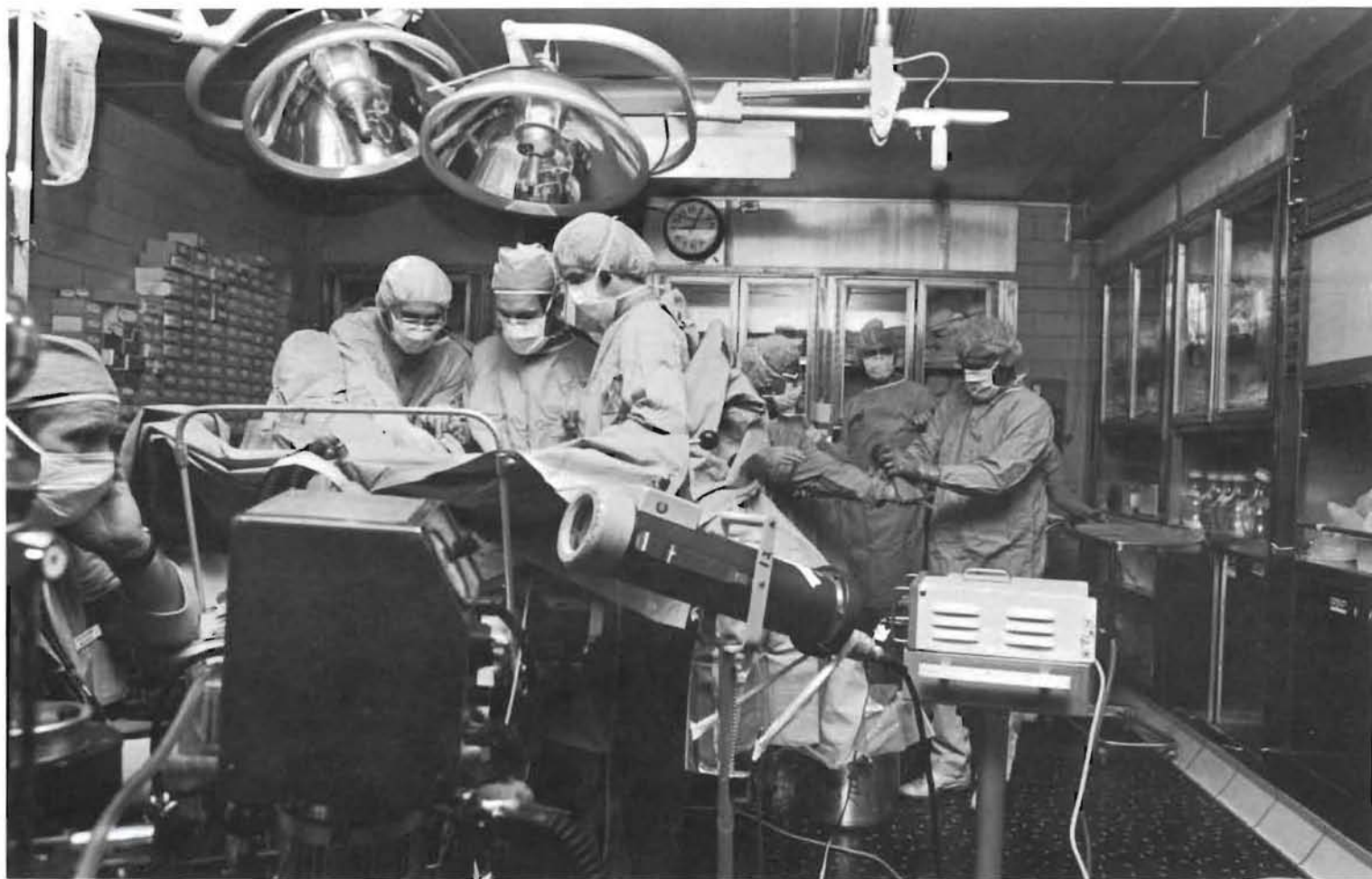
After a minimum of one year on hormones, the patient is referred to the surgical team. "We don't want people evaluated quickly, then rushing out and making an irreversible decision. We will not call them up at the end of the time period. They have to get in touch with us. We will make the referrals if they ask, but we don't try to convince them to have surgery," Packman says. If the diagnosis is made, the decision to have surgery is entirely up to the patient.

"We see a lot of patients from out-of-state. They must travel here for the evaluation, then, we can usually take care of subsequent problems and questions by telephone. When it's time for the hormone therapy, we locate someone in their community to administer it. In such cases our primary role is as a consultant," Packman says.

According to Packman, patients that he has seen having the diagnosis have ranged in ages from 12 to 58 years of age. "We don't begin hormone therapy until after puberty—usually age 18, and the earliest age for surgery is 21 years so that they can legally give informed consent for their own surgery," Packman says.

Some differences between male transsexuals, transvestites, and male homosexuals

	Male Transsexual	Transvestite	Male Homosexual
Gender Identity	Feminine	Masculine	Masculine
Dressing Habits	Feminine	Masculine + Feminine	Masculine
Sex Object Choice	Normal Males	Males + Females	Homosexual Males
Social Life	As a Female	As a Male	As a Male
Interest in Estrogen Therapy	Yes	Usually Not	No
Interest in Surgical Conversion	Yes	No	No



Charles Abbott Jamison has been on hormone therapy for 18 months. He has been wearing female clothing in public as well as in private and has found a vocation consistent with his feminine identity. He called today requesting a referral for surgical procedures.

The sexual conversion procedure for a male transsexual entails the combined efforts of Bucy, the urologist, and Wray, the plastic surgeon. The complete procedure takes from four to six hours and may be divided into four parts: penec-

tomy, castration, plastic reconstruction, and formation of an artificial vagina.

In the plastic reconstruction portion of the operation, scrotal tissue is used to form labia majora, and penile skin, labia minora.

An artificial vagina may be formed either from a skin graft from the thigh or by using the method of inversion of the penile skin or by inversion of both penile and scrotal skin. The skin of the amputated penis is stripped off and inverted like the finger of a glove.

The surgery is staggered. Wray begins by taking skin grafts from the thigh, hip or buttock area which are pre-

served in moist towels. Then, the patient is repositioned, and all the external genitalia are removed with the exception of a small length of urethra which has to be preserved. Thus an area is created in which the vaginal cavity will be placed.

Then, Bucy steps in to create the artificial cavity. "Much of this surgery is similar to doing some types of prostate operations," Bucy says. The cavity is made between the rectum and the prostate.

Once Bucy has completed the cavity, Wray fashions the

skin graft on a rubber mold which is then inserted into the cavity. It takes approximately ten days for the skin graft to adhere to the sides of the opening.

One year has passed since Monica Abbott Jamison's sex reassignment surgery. She returned today for her follow up psychiatric interview, and, to date, she is a poised and confident individual with a strong self identity. Monica Abbott Jamison has no regrets. Monica Abbott Jamison is a fictitious person who embodies many distinct characteristics of a transsexual.

What role does cholesterol play in our health? Does lowering it reduce the risk of coronary artery disease? These and other major health questions continue to be investigated through the many clinical trials of the Lipid Research Center.

Studying the Role of Lipids

by Glenda King Rosenthal

Between 1973 and 1976, 328 men in the St. Louis area made a commitment which was to affect their lives for the next seven years. That commitment was to the Lipid Research Center's Coronary Primary Prevention Trial (CPPT). These men, who were picked from a screening of 45,000, had to meet stringent criteria.

"They had to be age 35-59, have a cholesterol level of 265 milligrams per 100 milliliters of plasma, normal blood pressure (no higher than 140 over 90), and no previous history of heart disease or diabetes," explains Gustav Schonfeld, M.D. '60, director of the Lipid Research Center (LRC) and professor of preventive medicine and internal medicine.

"These men were picked to help us answer a major question: can heart attack be delayed or prevented in men with hypercholesterolemia—those who are at high risk for the development of coronary artery disease—by lowering the levels of cholesterol in their plasmas," Schonfeld says.

One of 12 across the country, the WUMS Lipid Research Center is funded by the National Heart and Lung Institute with an average of \$850,000 annually. A total of 3,810 men are participating in the study nationwide.

The participants were randomly assigned to two groups. One group takes cholestyramine, a drug which is known to lower cholesterol; the other group takes a placebo. Because it is a double-blind study, neither the participants nor the professional staff know which group is taking what.

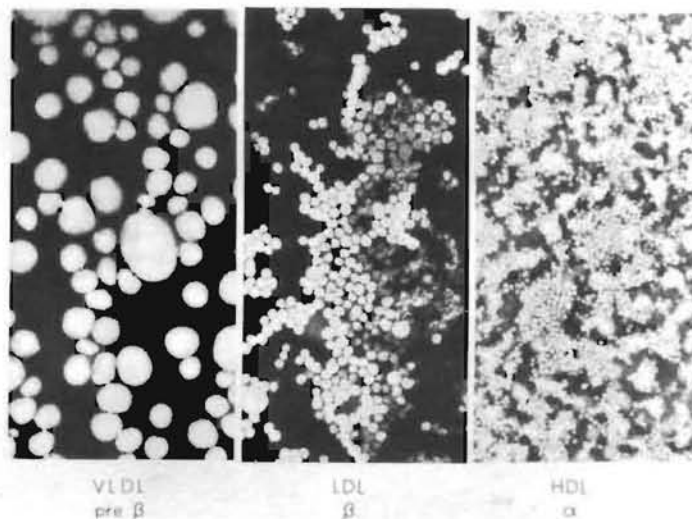
"In all the particulars, the two groups are identical," Schonfeld says. "For example, the mean ages, body weights, cholesterol levels, blood counts and blood chemistries of the drug and placebo groups are identical. It's important that the placebo and experimental groups be the same except for the medication they are taking. This has been a major pitfall in other studies and we wanted to make sure we avoided that."

Data on each participant is monitored by a Safety and Data Monitoring Board in Washington, D.C. Schonfeld describes the Board as an objective group of experts who meet every three to five months to review data.

"This group decides whether or not there are any significant trends," he says. "They could stop the study if it appears that we have sufficient data to determine that the medication does indeed aid in the prevention of heart disease. They also inform us if any participant is encountering a health problem. At the end of the study, all of the accumulated information will be reviewed with the participant and made available to his private physician."

Seven years is a long time to wait for results, especially for the men who have had to alter their lifestyles in order to participate in the study. For this reason, the problem of patient compliance is especially important, not only for the well-being of the participants but also for accurate study results.

PLASMA LIPOPROTEINS



Electron micrographs of the three major classes of lipoproteins which circulate in the blood.

"Patient compliance is a problem for all physicians who treat people with chronic diseases," Schonfeld says. "We have paid a great deal of attention to this problem throughout the CPPT study."

Maggie E. Noonan, adherence coordinator for the Coronary Primary Prevention Trial, deals directly with this problem. She has been with the study from its inception. "For the first two years of the study, I was responsible for the participants in terms of any counseling they needed for their problems with compliance," she says. "That was a patient load of 328 people and it didn't really work very well. We now use a team approach."

Each team consists of a dietitian and a physician assistant. There are now three teams, each following about 110 participants.

"This is a much more reasonable approach," Noonan says. "When the CPPT was designed, they didn't realize that counseling would be a necessary part of the study. It was thought that these men would comply with what was asked of them for the next seven years."

However, Noonan says literature on patient compliance indicates that only about 50 per cent of the people will follow medical advice. Fortunately, the CPPT's team approach has helped to keep adherence levels better than expected.

"We're dealing with middle-aged men, many of whom are at the peak of their careers," Noonan says. "Most of them have terribly busy schedules, which adds to the problem of compliance."

Participants are asked to comply with several things, the major two being following a special diet and taking daily medication.

"Each man is asked to take six packets of study medication per day," Noonan says. "The medication comes in powder form and is not particularly pleasant to take. It's rather gritty and lumpy if not mixed with enough water. Some men also experience gastrointestinal side effects."

"We ask the men to bring back their empty packets when they come in for a check-up. This is important so that we can determine how much medication they are taking. At that time, we also give them 400 more packets which should last them for the two-month period between clinic visits," she says.

All of the men are given the same diet to follow, although certain substitutions can be made to accommodate individual life-styles.

"The dietitians really have a big job modifying the diet to agree with individual participants," Noonan says. "The CPPT diet is similar to the one recommended for everybody by the American Heart Association. It was designed to lower plasma cholesterol by approximately five per cent. We had to choose a diet that these men could comfortably follow for seven years."

Even though the diet is not extreme in any sense, it does have an impact on a man's life.

Complying to this special diet is not always easy for the participants, particularly during the holiday season and vacation time. Noonan says the team does quite a lot of counseling during these times.

The wives of these men can also make a big difference in the success or failure of complying with diet and medication requirements.

"If we had it to do over again, we would have the wives play a larger role from the very beginning of the study," Noonan says. "If a wife isn't supportive, she isn't going to cook the required diet, nor will she encourage her husband to take his medication. She might even have a negative effect by telling him the medicine isn't doing him any good. If she doesn't understand what the study is trying to accomplish, it's difficult for her to understand why her husband puts up with any discomforts or side effects," she says.

The inconveniences of the study have been one of the contributing factors in the CPPT's dropout rate. The dropout at the WUMS Center, however, has been much lower than the anticipated five per cent a year.

"When the study began four years ago, we had 328 participants," Noonan says. "We've only had 21 men drop out, which isn't even close to the five per cent a year predicted rate."

When conducting a clinical trial, it is extremely important to complete the study with the same number of participants as when it was begun. If people leave the study, the results can be biased.

"Because of this," Noonan says, "we do our best to keep track of all the participants. We call the men who have left the study every six months just to see how they're doing."

This personal approach to the individual participant has contributed a great deal to the CPPT's low dropout rate.

"Participants are asked to come to the clinic every two months," Noonan says. "If they miss the appointment, we have several people who are responsible for calling them. The longer a person is out of the program, the harder it is to get him back and into the routine."





Gustav Schonfeld, M.D., Lipid Research Center director, and Barbara Pfleger, research instructor in preventive medicine, in one of the laboratories of the LRC.

Pat Basich, cardiology technician, and Ali A. Ehsani, M.D., assistant professor of medicine, examine a CPPT participant after a graded exercise test. Jackie Woods, cardiology technician, operates the EKG machine.

Noonan says the health professionals involved in the CPPT study will go to almost any length to keep participants in the study. "In fact, Dr. Joseph Witztum, project coordinator of the CPPT, drove fifty miles at 5 a.m. to run tests on a man who said he didn't have time to come to the Clinic. This kind of concern impresses upon the participants that we're very serious about their involvement in the study."

If a participant leaves the St. Louis area, he is asked to commute to the Center nearest his new home. "We just had one of our men move to Alaska and he now goes to the Seattle clinic. A man who was formally with the Johns Hopkins' Center now commutes here from Tennessee," Noonan says.

"Our participants receive excellent care," Noonan says. "Each person comes in six times a year and it costs the LRC approximately \$4,000 a year to support each individual."

These men develop a rapport with the professionals in the LRC because they see them frequently. They also are seen for at least an hour, sometimes for up to three and a half hours.

"We become personally involved with our participants, which is probably one of the reasons we have successful compliance," Noonan says. "We sponsor social events so the participants can get to know each other and share common problems. We also have a newsletter in which we share LRC news with them, give them low cholesterol recipes, review restaurants where they can order the required diet and profile different participants. We really are a part of their lives and having a strong rapport with these men is good for them and the study," she says.

At the end of seven years, the men in the Lipid Research Center's CPPT will have had a major role in answering an important medical question: does the lowering of cholesterol decrease the incidence of heart disease?

"In order for this question to be answered, the men must be committed to the study and we must be committed to them," Noonan says. "This has been the case throughout the study; it's been gratifying to be part of it."

According to Schonfeld, the Coronary Primary Prevention Trial is the largest clinical study being conducted at the Lipid Research Center. "The CPPT entails the most time and money and involves the most people," he says. "However, important clinical and basic studies in other areas of lipid research also are underway in the laboratory. There are studies in the synthesis and secretion of lipoproteins, on the immunology and structure of the proteins in lipoproteins and on the interactions of lipoproteins with cells."

The problem of hypercholesterolemia is not limited to adults, and one important study involves 23 children. The study, which is funded by The Upjohn Company and the National Institutes of Health, is analyzing the effect of colestipol in the treatment of hypercholesterolemia in children.

"Hypercholesterolemia is recognizable in children as young as one year old," Schonfeld says. "These children, who come



Maggie E. Noonan, adherence coordinator for the CPPT, keeps track of the status of each participant by keeping their names on a magnetic board in her office.

from families whose members die from coronaries at an early age, are particularly susceptible to the development of atherosclerosis early in life. We hope to be able to prevent these children from developing this problem later in life.

"Since we know hypercholesterolemia is very frequently an inherited condition, we suggest to adults who come here to have their children examined."

Schonfeld says the study also includes children who have been referred by their private pediatrician. "It's becoming more and more common for pediatricians to test a child's cholesterol level, which should help us to prevent future problems," he says.

Because the medication given to these children interferes with the absorption of fats, the study analyzed whether or not vitamin levels were affected.



Janet Kolar, physician assistant in the LRC, takes a patient's blood pressure during a routine physical examination.

"Basically we're attempting to determine the long-term safety of these drugs on children," Schonfeld says. "Fortunately, the medication does appear to be effective with no ill effects."

In addition to studying the effects of colestipol on children, Schonfeld says they are also looking at behavior in terms of compliance with medication. "To get a child of seven or eight to stick to a diet and to take medication is even more of a problem than it is with an adult," he says. "So in this study we're using different behavior modification techniques to aid in solving this problem. We've learned that the best way to handle the problem of compliance, in both adults and children, is to be skilled in analyzing the particular problems that keep people from complying. We then apply the proper behavior modification techniques for that individual."

Another major research effort of the Lipid Research Center involves the study of familial hypercholesterolemia, or Type II hyperlipidemia. In addition to the Coronary Primary Preven-

tion Trial, this area is of particular interest to Joseph L. Witztum, assistant professor of medicine and project coordinator of the CPPT. His research is funded by the National Institutes of Health and Dow Chemical Company.

"I'm interested in studying the effects of bile sequestrants, which are the principal drugs used in treating hypercholesterolemia, on lipoprotein metabolism," Witztum says.

"We have found that these agents not only lower cholesterol but they also cause qualitative alterations in the lipoprotein structure. These changes may effect the way in which lipoproteins interact with the cells."

Witztum says these changes would not normally be discovered in the private physician's office. "This kind of problem can only be determined through a research effort, and the LRC is one of the few places conducting research in this area."

"When we find the person with high cholesterol, we want to find the best mode of therapy for him. Our research in Type II hyperlipidemia is on-going," Witztum says.



LRC dietitian Susan Grimes discusses diet with one of the participants in the Coronary Primary Prevention Trial.

Another major research effort funded by the National Institutes of Health, the American Heart Association and Ayerst Laboratories, involves the study of Type III hyperlipidemia, an unusual form of hyperlipidemia characterized by high levels of triglycerides and cholesterol in the blood. Studies in this area have focused on the diagnosis of Type III, determining the mode of inheritance and analyzing the effects of therapy.

Schonfeld says people affected with Type III also have atherosclerosis, particularly in the vessels which carry blood to the lower extremities.

"People with severe cases of Type III have difficulty walking because the blocked arteries do not allow adequate flow of oxygenated blood," he says. "When the symptoms become severe enough, surgery is frequently necessary. Many of these people develop coronary artery disease at a young age."

A lipoprotein has been discovered in the blood plasma of these people which is abnormal both in the fats and proteins it contains. "In fact," Schonfeld says, "one of the proteins (ApoE-III), which may be important for the normal transport of fat in blood, appears to be missing."

Stuart W. Weidman, Ph.D., assistant professor of biological chemistry in preventive medicine and director of the Core Laboratory, has perfected a technique to determine whether or not this ApoE-III protein is missing. "If a patient is referred to the LRC because he has high cholesterol and triglycerides and we discover a pattern of lipoprotein distribution suggestive of a Type III disorder, we would then utilize the very specialized tests Weidman has developed," Schonfeld says.

If a person is discovered to have Type III, a screening of that person's family is done. Thus far researchers in the study have found 15 families affected by it.

"Weidman's technique has allowed us to discover how Type III is inherited and to offer genetic counseling and the appropriate treatment to affected families," Schonfeld says.

Weidman's technique also has proven to be useful in identifying the Type III disorder in young children. "We can now institute the appropriate treatment early in life. Unlike the men in

the CPPT study who have Type II where we do not as yet have the answers, we are fairly confident that treating Type III hyperlipidemia will prevent vascular complications later in life," Schonfeld says.

Fortunately, we have discovered that of all the lipid disorders, Type III hyperlipidemia responds best to both diet and drug therapy. The levels of the 'bad' cholesterol (VLDL and LDL) fall and levels of 'good' cholesterol (HDL) rise."

Research efforts at the LRC also involve studies on hyperlipidemias characterized by high triglycerides rather than cholesterol and the relationship of lipoprotein metabolism to diabetes and obesity.

"The lipoprotein disorders of patients with renal diseases are being studied by Andrew Goldberg, M.D., assistant professor of preventive medicine and internal medicine," Schonfeld says.

"These are important studies because the most common cause of death for hemodialysis patients and for diabetics is cardiovascular disease. These people have a high prevalence of lipid abnormalities."

Another study which could have wide spread ramifications is funded by the National Institutes of Health and Ralston Purina. There have been reports that using soy protein in the diet, rather than animal protein, lowers the level of cholesterol. Researchers at the Lipid Research Center are testing that theory.

We are also testing the effects of diet, drugs and various combinations," Schonfeld says. "These studies, funded by the NIH and by various pharmaceutical companies, are teaching us how to sharpen the indications for therapy and to identify clinical situations in which various diets and drugs will be useful."

Even though physicians at the Lipid Research Center do see patients on an individual basis, they encourage them to participate in one of the several on-going clinical trials.

"The majority of our patients have either participated in the past or are currently participating in some sort of diet or drug trial," Schonfeld says. "This gives us the opportunity to develop rational, organized approaches to therapy."

Hopefully, this organized approach will aid in designing successful, specific treatments for the millions of people who suffer from the various forms of hyperlipidemia.

In the United States, a conservative estimate is that approximately 7.8 to 8.5 per cent of the population is phobic to some degree. This means that around nineteen million Americans are afflicted with phobias. Of these, approximately eight million are severely disabled because of their problem. Fortunately, health professionals are now recognizing phobias as a serious concern which can be treated with a variety of methods and ultimately cured.

OVERCOMING FEAR

By Glenda King Rosenthal

"I can go to a shopping center if I really have to, but it does make me extremely uncomfortable. I get panicky feeling, as if I were going to faint, before I get back home. If someone goes with me, I don't feel nearly as bad. I know they can take care of me if something does happen."

Edna Taylor is 48 years old, the wife of a successful businessman, and the mother of two adult children. She and her husband live in a large, well-appointed home—a home Edna rarely leaves. Her contact with the world outside of her home is mainly limited to the telephone and television.

Edna has agoraphobia. It is one of the more common phobias and can be defined as the fear of being away from familiar and supportive surroundings.

Edna is one of millions of people who suffer from the chronic anxiety and abnormal fear that is called phobia. Even though the word has been with us for less than 200 years, the existence of "fear sickness" has been known for centuries. The origin of the word stems from Phobos, the son of Mars and Aphrodite in Greek mythology. He accompanied his father, the god of war, into battle to instill fear in the enemy.

It is not uncommon for people to experience discomfort in certain situations, such as in confined spaces or at great heights, or when confronted with a snake. Fortunately, few of these mild fears develop into an intense phobia which can limit the afflicted person's way of life.

A true phobia, as opposed to a mild fear, has several properties: it is out of proportion to the situation; it cannot be reasoned away; it is beyond voluntary control, and it leads to avoidance of the feared object or situation.

According to Richard Wetzel, Ph.D., assistant professor of medical psychology, the phobic is not insane or lacking in willpower. "Unfortunately," he says, "too many people, health professionals included, do not take phobias seriously enough. The phobic usually realizes the irrationality of his fears, but still feels compelled to avoid the feared situation."

Edwin B. Fisher, Jr., Ph.D., associate professor of psychology, agrees with Wetzel. "If a person feels his fear is strong enough to seek treatment, then it is a problem for that person and should be taken seriously," he says.

"The critical thing is not whether a fear is extreme; the critical thing is whether it's a problem for the person and affects his life."

More critical than the extent of the fear is the coincidence of the fear. A person with a mild fear of snakes who lives in a snake-free area has a simple problem. But one can easily imagine circumstances in which the problem could become pronounced.

This concern for the individual patient and his problems is basic to the Behavior Therapy Clinic, which is part of Washington University's Psychological Service Center. The Center provides a number of services, including research, graduate training, service to the community, and opportunities for faculty private practice.

"The Behavior Therapy Clinic has been active for almost two years," Fisher says, "and during that time we have treated many people from all walks of life. We see quite a few people for fears, both in individual therapy sessions and in clinic situations, such as speech and exam fear clinics."

The clinic sees people with many different types of fears and treats a variety of people, children as well as adults. For most of these people, their phobia appeared gradually; in fact, the majority of them cannot remember how or when it began.

"Most phobias are learned, and it appears that some of them are simply not unlearned," Wetzel says. "Animal phobias are a type of phobia that appear rather infrequently, and there is evidence to indicate that children and adults with animal phobias have mothers who are afflicted with the same fear."

Wetzel says there is a strong possibility that all little children are afraid of such things as thunderstorms, rats and snakes. However, in most cases they unlearn the fear because the mother reassures them that there is nothing to be afraid of.

"If the mother has the same fear," he says, "she could be teaching the child to fear it through example. Or, she could be teaching the child a fear simply by doing nothing to discourage it."

With most other types of phobias, evidence also indicates that there is an early propensity towards it. "Of course there is the situation, such as being trapped in an elevator, in which the person is subsequently fearful of elevators," Wetzel says. "However, most fears develop over a period of time rather than with one cataclysmic event."

In many instances, people are fearful of something they have never encountered. Fisher says a good example of this teaching of fear is the effect the movie "Psycho" had on people. The scene in which a woman taking a shower is brutally stabbed to death is indelibly etched on many people's minds.

"I think over half of the people who saw this movie sometimes experience varying degrees of discomfort when showering alone at home," Fisher says. "I know this has certainly been true of the people in my lectures."

"Of course, none of these people has ever been stabbed while showering, but the lighting, sound, camera angle and pace of the movie taught people fear," he says.

"I know there are people who can trace their strong aversion to taking a shower when alone to the time when they saw this movie. Fears can be learned vicariously, and they can be unlearned in the same manner."

Phobias may be divided into types: agoraphobia, social phobia and animal/object phobias. Of the three groups, agoraphobia is seen most frequently by both Wetzel and Fisher. "Since we have been running the behavior therapy clinic," Fisher says, "about half of the people we have seen have been classifiable as agoraphobics."

The agoraphobic tends to be very timid, lacking in self-confidence and very much afraid of fear. They frequently have

acute painful experiences, or severe anxiety attacks, and are very much afraid of having one.

"For example," Fisher says "the agoraphobic may not be afraid of driving or being outside, *per se*, but afraid of driving and having an attack. The problems often arise when they are away from their home but, on closer examination, the fear is of being on their own, even though they might be saying they're afraid of driving. The specific fear, such as the fear of driving or of shopping malls, usually is masking something a bit more general or abstract."

The agoraphobic frequently has a fear of abandonment and a perceived inability to cope with life on one's own. Although not exclusively, most agoraphobics are women. Women who are housebound suffer more from this than any other group.

"Frequently agoraphobia affects a woman who is at a point in her life when her role as homemaker is diminishing," Fisher says. "Her children are leaving for one reason or another and she now has the burden of hours. People don't depend on her as they once did, and many times this comes at a point in her husband's career when he is working a 14 hour day and loving it. So, for the first time in many years, this woman really is left on her own," he says.

Wetzel, who runs a therapy group for agoraphobics, says many times these women will come for therapy saying they never were afraid of anything and now are afraid of everything. They are also frequently misdiagnosed as depressed.

"Even though the woman in therapy talks about being afraid of shopping or some other out-of-home activity, at some point she realizes something much larger is wrong," Fisher says.

Wetzel and Fisher agree that for this reason it is important for the family of the agoraphobic not to minimize the problem. "When the family insists that the problem can be easily overcome, this often intensifies the woman's fears because she knows the problem is beyond simply 'getting over,'" Wetzel says.

Frequently the family of an agoraphobic will unintentionally behave in an ineffective way that is detrimental to the person affected. The family's attempts at reassurance may be viewed by the patient as belittling. "The problems these women face are not to be simply gotten over," Fisher says, "they are to be dealt with."

It is not easy to live with an agoraphobic. Many people find it difficult to understand why something as common as leaving the house can elicit fear.

"But the family can help," Wetzel says. "We try to encourage the family not to reinforce the fears of the agoraphobic by always doing things for her. Of course they should up to a point, but in treatment it's necessary for the person to begin doing things by herself. We keep the family informed of what should be done next. We want the family of the agoraphobic to encourage the person to move ahead at her own pace."

It is believed that agoraphobia is more common in women because men are traditionally taught from an early age that they must go out into the world and earn a living. Wetzel says they are also less likely to admit that they have a problem.



Drawing by Francisco Goya circa 1800.



Animal/object phobias are also more marked in women than men. Of the animal phobias, the most common fears involve snakes, rats and mice, birds and feathers, bees and wasps, and cats and dogs.

Fisher emphasizes that it is not at all uncommon for a person to feel squeamish or uncomfortable when handling a snake or to duck when a bee is flying around. "But few people will actually turn pale at the thought of swatting a bee," he says. "Again, it is a matter of degree. If the fear of an object or animal begins to affect a person's life-style, then we must view it as a problem and treat it as such."

According to Wetzel, animal/object phobias are easier to treat than agoraphobia and social phobias. "In most cases, animal/object phobias are more of a nuisance to the person affected rather than a real disability such as the case with agoraphobia," he says.

"Most people who have a fear of a specific situation, such as being trapped on an elevator, or of an animal have never actually had a bad experience with it. The possibility of having a bad experience elicits fear in people as much as actually having it," Wetzel says.

"However, if a person is fearful enough of something to desire treatment for it, then we feel their response is strong enough to justify that treatment."

This same philosophy is true for the social evaluation phobic. It is not uncommon for a person to feel uncomfortable in a room full of strangers or when taking an examination. However, when the fear of a situation begins to affect the way a person lives his life, treatment should be sought.

"A social phobic is someone who becomes very uncomfortable in a situation in which he thinks he might make a fool of himself," Wetzel says. "Many people have a fear of looking foolish or being criticized, but most of us don't have the physiological responses that go along with a phobic reaction. It's a matter of degree."

Fortunately, there are several modes of treatment which can greatly aid the person afflicted with any of the three categories of phobias. The two most frequently used methods are desensitization in imagination and *in vivo*.

Wetzel says desensitization in imagination involves constructing a hierarchy of situations in which the phobic is least anxious to most anxious. This desensitization process is conducted in the therapist's office; with desensitization *in vivo* the phobic actually confronts the feared situation away from the office. Patient relaxation is integral to the success of either method.

"We view the problem of fear as a problem of the way in which a person is behaving," Fisher says. "It is important to remember that fear is not simply something that is happening to a person. It is something he is doing, although not willfully. So, we have to teach that person another way of acting in a particular situation. The critical aspect of acting in a non-fearful manner is learning to act with some degree of relaxation and control," Fisher says.

Consequently, Fisher views desensitization as teaching a person new ways to act in a situation. The first step in this teaching process is extensive relaxation training.

"Before we discuss the fearful situation," Fisher says, "the person must first learn to relax. "Most of the literature indicates that biofeedback, forms of self-hypnosis and various forms of meditation all have similar relaxation effects.

"We use a muscle tensing-relaxing method primarily because it emphasizes to the patient that this is a skill he can do himself rather than something we do to him," Fisher says.

The goal of relaxation training is to get the patient to learn to relax on his own and not be dependent on the therapist. He can then transfer this ability from the therapist's office to his own life.

"The critical thing in relaxation training is for the person to learn to spot very slight bits of tension and learn to relax it away before it gets out of hand," Fisher says.

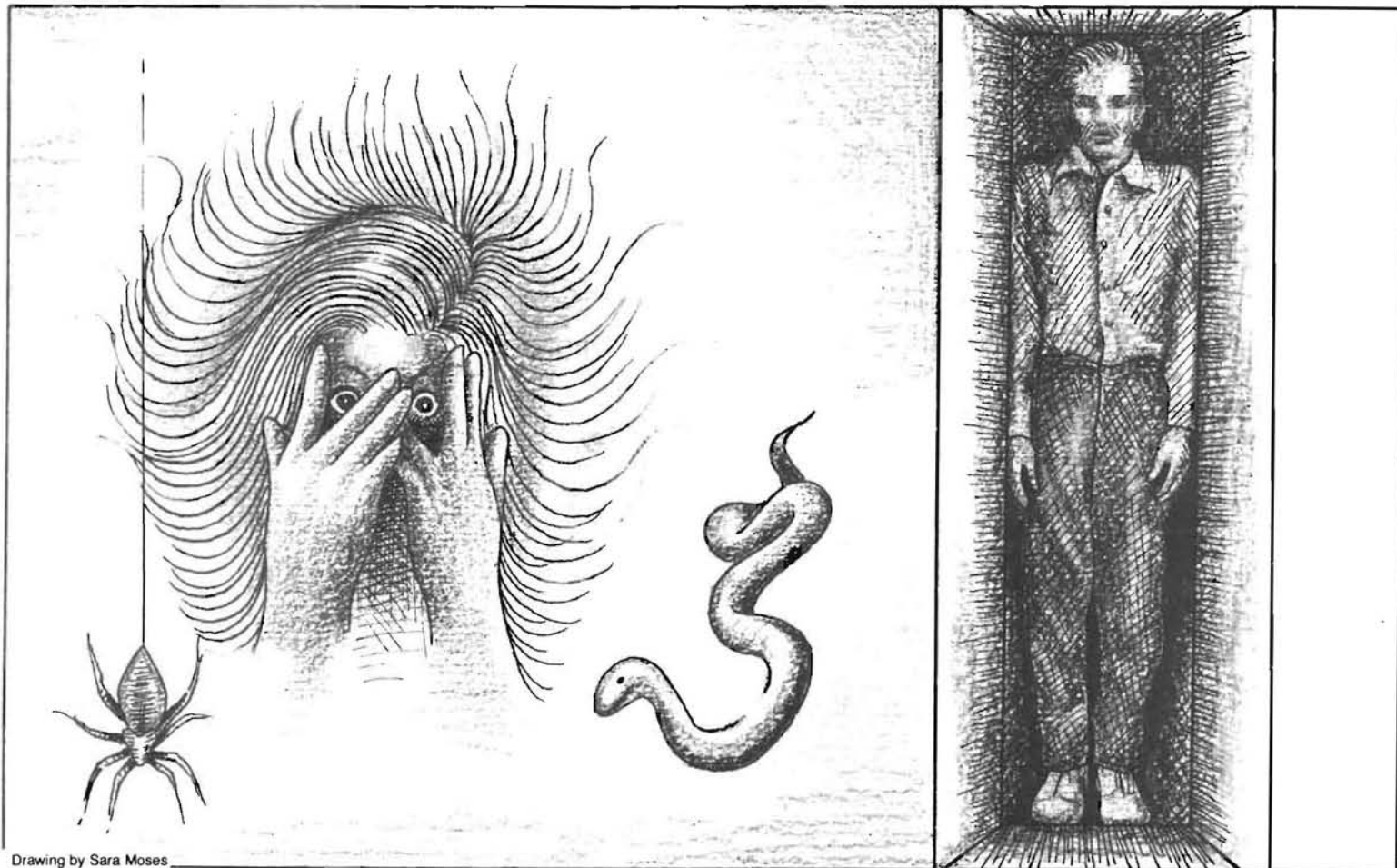
After the patient has been taught the desired behavior, the next step is to teach him to use that behavior in a specific situation. "Of course we can't bring airline terminals or people's showers into the office, so we use imagination as a means of bringing the feared situation into the office," Fisher says.

Wetzel says when people are relaxed with their eyes closed, it is possible for many of them to imagine things quite clearly. "Psychologically, it is as if they are actually in the fearful situation," he says. "The *do* feel fear."

The patient is asked to imagine the fearful situation and then practice using the relaxation method as a means of coping with the fear the situation elicits.

"We usually begin desensitization therapy by having the patient imagine coping with the tension by relaxing in situations that are related to the fear but are not terribly anxiety provoking," Fisher says. "For example, if we were dealing with an airplane phobic, we might start off by having him imagine that he was planning on taking a plane trip. We would then have him relax away the tension of that thought. The next step on the hierarchy might be having him imagine that he is in line at the ticket counter at the airport. But before we would have him move to a different level on the fear hierarchy, we would make sure he is comfortable where he is. Starting with the least fearful situation on the hierarchy is usually most palatable for the patient. It makes sense to walk before you run."

Wetzel and Fisher both agree that they view the role of the patient as active rather than passive. The role of the



Drawing by Sara Moses

patient is to learn to cope with anxiety by actively using relaxation as a coping skill. The patient must continually practice relaxation throughout the treatment by imagining scenes and learning to relax away the tension the scenes create.

"The critical thing is not that a scene not produce any tension but that the patient is comfortably able to relax away the tension," Fisher says. "In latter stages of desensitization treatment, we encourage patients to allow themselves to become tense. By doing this, they learn that tension is indeed something that they do to themselves and have the power to control."

As the treatment progresses and the patient becomes comfortable in dealing with his fears in imagination, the therapist then gives the patient instructions for practicing dealing with his fears away from the office surroundings.

"We usually wait until the treatment is underway in the office before we begin desensitization *in vivo*," Wetzel says. "We then ask the patient to begin making small steps outside. We want him to do things he is comfortable doing, and most importantly, we want him to do things he can do on his own and not be dependent on the therapist."

As with desensitization in imagination, a hierarchy of fears is constructed and the patient is asked to move through it step by step.

"I recently treated a man with airplane phobia," Wetzel says, "and we constructed a hierarchy for him. We began by simply having him go to the airport and watch a plane take off. The final step on the fear hierarchy was actually having him go on board a plane. The airline allowed him to go onto the plane and the crew explained all of the procedures to him. This man did this in anticipation of his first plane flight, and he did manage to do it. After that first trip, he was able to take subsequent ones."

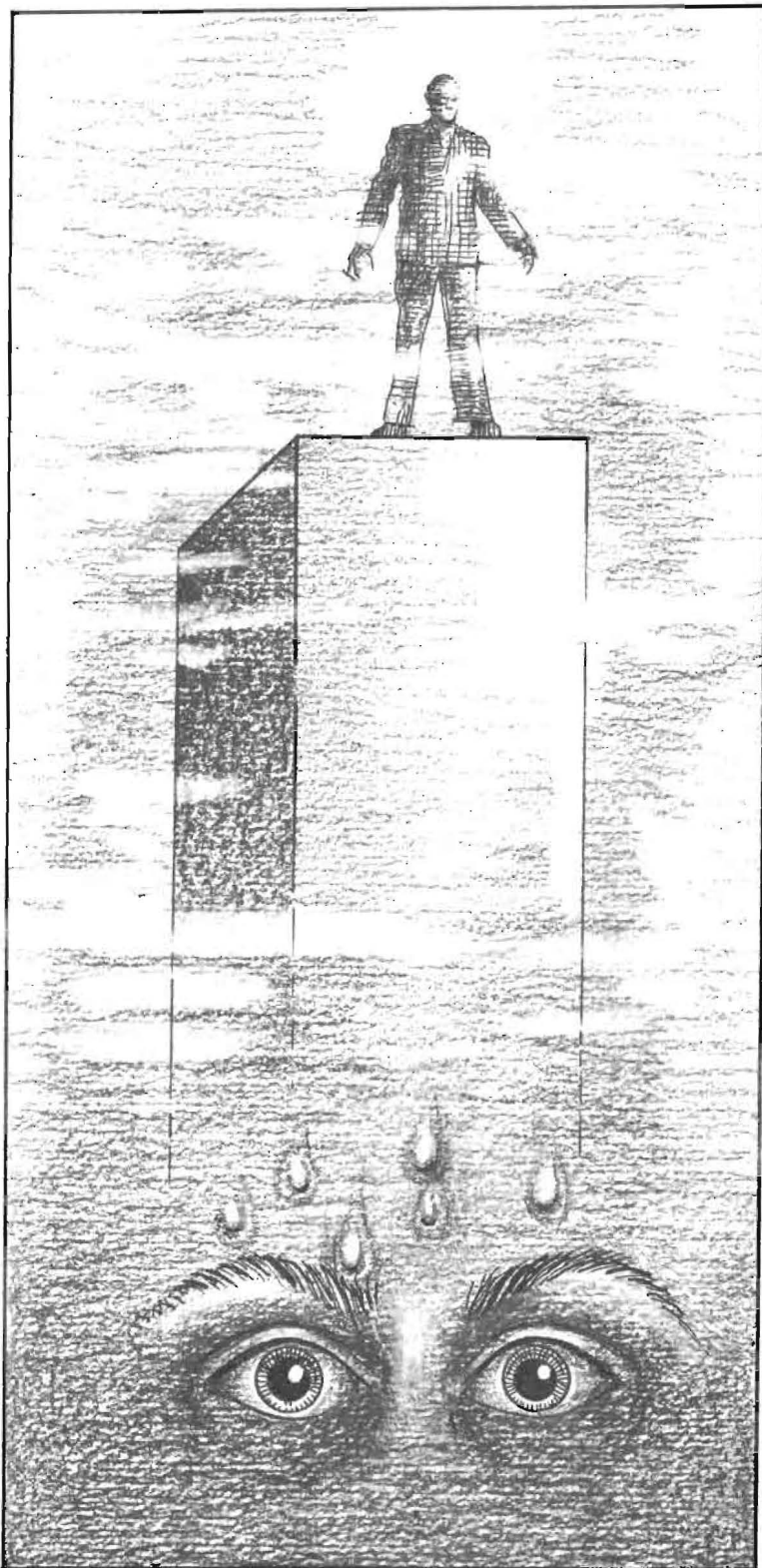
Fisher and Wetzel say that towards the end of desensitization therapy, they might work with a patient to get him to be able to talk himself out of inappropriate reactions. In many instances, it can help if the person has "coping instructions."

"If a person is afraid of being trapped, for example," Wetzel says, "I would help him develop a series of sentences that would aid him in coping with a fearful situation. They might say 'I am not trapped'; 'I can always get out'. By using this coping technique, the person has a way to reassure himself and calm down. You can't tell someone he'll never get stuck on an elevator, but you can give him a different perspective. This would then make it easier for him to ride on an elevator," Wetzel says.

At the end of desensitization therapy, the phobic is still capable of feeling arousal when he is around the feared object or in the anxiety producing situation. However, he is able to control the fear.

"And it seems that by feeling comfortable that he can control the fear should it arise," Fisher says, "it simply arises less often. In many instances, fear triggers fear."

Wetzel and Fisher say that desensitization therapy works quite well for people with specific phobias, such as animal or situational phobias. However, it does not always work as well



Drawing by Sara Moses

for people afflicted with agoraphobia. "It's very difficult to construct a fear hierarchy for the agoraphobic because he is afraid of so many things," Wetzel says.

Implosion, or flooding, and self observation are two treatment measures which have been effectively used in some cases of agoraphobia. Implosion involves barraging the person with the feared stimulus to the point where it loses its ability to cause fear.

"Implosion can be done in imagination or *in vivo*," Wetzel says. "The idea is to make the person confront his fear and not allow him to run away from it. If one is going to treat with the implosion method, it has to be kept up until there is a reduction in anxiety. It can appear to be a rather traumatic way of treating someone because usually these people have never been forced to confront the feared situation.

Self observation has mainly been used in the treatment of agoraphobia. Wetzel describes this method as self-testing. "The agoraphobic might be told to go out of the house for as many minutes as she is comfortable," he says. "As soon as she begins to feel anxious, she should come back and write down how many minutes she was out. The next day she would attempt to beat that time. This is done repeatedly during an agreed on period of time each day. In this way she will gradually increase her time. We ask the agoraphobic to begin with a small task and gradually work up."

Agoraphobics need to learn more effective skills and coping techniques, according to Fisher. He encourages them to become involved in activities as a means of showing them that they can indeed take care of themselves.

"We often concentrate on graded assignments to get the person more active," Fisher says. "We want her to do things that make her feel good about herself and increase her feelings of self-worth.

"Many times we don't work directly on the specific fear, for example, because after discussing the problem it becomes apparent that the fear is really a reaction to deficits in other areas," he says.

What Fisher may work on is getting the agoraphobics involved in other activities, such as getting a job, joining an organization or doing things to enrich their marriages. All of this is done to encourage more of a sense of identity.

"The agoraphobic usually has a fear of being lost and left to her own devices," Fisher says. "Frequently the fear diminishes as the person becomes involved in new things and gains a sense of efficacy and identity."

Research indicates that agoraphobics have stronger autonomic reactions than do people afflicted with other types of phobias.

"In a phobic situation, the body prepares for fight or flight," Wetzel says. Adrenalin and epinephrine are pumped into a person's system, heart rate increases, the skin begins to tingle, and the person may feel dizzy and light headed. These are all symptoms of an anxiety attack."

This flight or fight reaction is extremely uncomfortable and is often the true fear behind a phobia. People are simply afraid of being afraid. They are afraid of the somatic correlates of fear, and in many instances, this is what a person must be deconditioned to.

"In deconditioning a person," Wetzel says, "we must emphasize to them that he is simply afraid. All of the signs he is experiencing do not mean he is going crazy or going to lose control and do something embarrassing. It's important for the person to realize he is simply having an anxiety reaction as part of the phobia. A non-phobic person would have the same reaction if he met a tiger out on the street."

Wetzel says the real issue in treatment is to find out what the person is afraid of. "I spend as much time getting people to examine what they are afraid of as I do getting them over the hurdle and actually treating the fear," he says.

"If a person expresses fear over being on an elevator, the fear may not be of the elevator but of being trapped. The same could be true of a person fearful of airplanes. In these cases, what the person needs to be desensitized to is the fear of entrapment, rather than an elevator or airplane," Wetzel says.

Successful treatment for phobics can vary from eight sessions to more than 20. According to Wetzel, specific fears and social fears are easier to treat than agoraphobia. "Agoraphobics spend a great deal of time worrying about simply being afraid," he says.

Wetzel and Fisher both emphasize that the person suffering from a phobia is not insane. Consequently, the patient himself can be a good judge of what treatment method is best for him. "I tell the patient all of the treatment options we have and discuss the advantages and disadvantages of each method with him," Wetzel says. "Since these people are competent and are the ones that have to do the work, I feel this is the best way. They usually know which treatment method they would feel most comfortable with."

The phobia patient is essentially treating himself. The therapist acts as an advisor by telling the patient of different treatment methods and directing the therapy.

"The phobic treats himself with our help," Wetzel says. "It takes time, effort and a desire to do something about the condition. The person suffering from a phobia can be helped. There is no need for someone to live a life incapacitated by a disabling fear."

Newly Studied Bone Marrow Transplant Technique Shows Promise

By Katherine S. Robbins

Bone marrow transplant research dates back to the 1930s. However, a relatively new area of research eliminates the major obstacle of finding a matched donor by extracting the patient's own marrow during remission and freezing it until it is needed. Geoffrey P. Herzig, M.D., assistant professor of medicine, is involved in this area of research with the support of the Division of Research Resources of the National Institutes of Health, and the Leukemia Society of America, Inc.



A beaker of bone marrow cells sets on a stirring apparatus.

The use of bone marrow transplants in the treatment of leukemia, aplastic anemia and related cancers has begun to produce encouraging results. There are, however, physical risks for the recipients of another person's bone marrow. Also, as a recent court case in Boston showed, heart-rending conflicts can arise over the rights of tissue donors to refuse to participate in the transplant procedure.

An alternative technique is currently being studied by Geoffrey P. Herzig, M.D., assistant professor of medicine. It involves freezing and storing an individual's own bone marrow and transplanting the stored bone marrow back into the individual at a later stage of treatment.

According to Herzig, who came to WUMS in 1975 from the National Cancer

Institute, clinical research with bone marrow transplantation began in the 1930s based on the results of studies which showed that circulating blood cells are made by bone marrow. At that time transplants were attempted on individuals who suffered from conditions which affected blood cells such as leukemia and aplastic anemia. Success was achieved in several instances when an identical twin donor was available. However, the majority of the transplants were unsuccessful because recipient and donor had not been "matched" and the recipient's immune system continued to function normally to reject the foreign bone marrow.

"A very high degree of matching is required," Herzig says. "In order for the transplant to take, not only does the bone marrow have to be matched for major histocompatibility (HLA) antigens, but the

immune system of the recipient has to be suppressed," he explains.

Before Herzig began his investigations, with few exceptions, the only people who could be matched closely enough were brothers and sisters. Because HLA antigens are inherited, siblings have a fair chance of having compatible HLA antigens. "HLA typing of the family also involves doing what is called a mixed leukocyte culture in which the blood cells of the potential recipient and donor are mixed together in a test tube and allowed to interact," Herzig says. Incompatibility can be recognized because it results in cell division in the culture.

"Once a suitable donor has been found, the transplantation procedure involves removing the bone marrow from the donor by inserting needles through the skin into the bone marrow cavity," Herzig continues. "The hip bone is generally used because of its size and the fact that a large proportion of the total bone marrow in an adult is found in that area."

Bone marrow in its normal state is a gelatinous, fatty mixture that can be aspirated with a syringe; approximately one pint of bone marrow mixed with blood is removed. "It is filtered through a fine mesh stainless steel screen to remove any clumps or particles of bone until it is essentially a suspension of cells in plasma," Herzig says. "It is then given to the recipient by intravenous transfusion. The immature cells, or stem cells, home to the bone marrow cavity where they multiply to repopulate the bone marrow and begin production of mature blood cells which are released into the circulation," he says. Herzig says that because only about one per cent of the donor's bone marrow

is removed, there is virtually no effect on the function of the donor's bone marrow.

As only a small number of individuals can find a matched donor, there has been natural encouragement for the research alternative currently being studied at WUMS: freezing an individual's own bone marrow for their own future use after intensive treatment for leukemia or other malignancy.

A young Illinois lawyer, James D. Monroe, was among the first to receive the benefits of Herzig's techniques. Monroe was introduced to the technique in January of 1977. "I had graduated from New York University Law School in June of 1976 and during the summer had experienced a lot of fatigue and tension from what I thought were the stresses of studying for the bar exam," Monroe says.

Immediately following the bar exam he went to Colorado on a long-awaited vacation where he tried to climb a 14,000 foot mountain from an 11,000 foot base camp. "I was in agony. My muscles ached and I had to strain for every breath. I thought maybe there was something wrong with my heart because I had an accelerated pulse rate," he says.

On his return to the St. Louis area a routine physical exam disclosed that the problem was with his blood, not his heart. On October 11, 1976, Monroe was diagnosed as having acute myelocytic leukemia. Herzig placed him on conventional chemotherapy and two and a half months later he was in remission (when the blood and bone marrow return to a normal appearance.)

"Once I was in remission," Monroe says, "Herzig gave me two options. First, he told me what I could expect with some confidence from

accepted maintenance drugs, because he knew the statistics. Because initial HLA typing of my mother and sister showed we weren't compatible, my only other option was the bone marrow autograft. Herzig was more cautious in predicting my chances with the autograft because it was a brand new protocol. He is always cautious with an individual's feelings," Monroe comments. "He is aware of the emotional burden of his diagnosis, and he doesn't ever want to raise one's hopes too high only to let them down. Still, he was cautiously optimistic. So I consented to the new treatment," he says.

According to Herzig, transplantation with the freeze-preserved bone marrow protects against bone marrow suppression which is a side effect of most cancer therapy. There are several advantages in using an individual's own bone marrow. One, it eliminates the requirement for a matched donor, and, two, it eliminates the problems of graft rejection and graft versus host disease which can occur in sibling transplants despite HLA matching.

Graft versus host disease is a major potential problem. At times the bone marrow graft fails to take or is rejected by the recipient's immune system. As both the recipient's bone marrow and total immune system are replaced with donor cells, there is the possibility of an immunological attack by donor cells against the foreign tissue antigens of the recipient. "Nearly 80 per cent will show signs of graft versus host disease, and about 20 per cent will die from it," Herzig says.

"Recipients who reject their grafts usually die because of bleeding or infections due to the failure of the bone marrow to produce platelets and white blood cells," Herzig continues. "With leuke-



mia the transplanted bone marrow may also fail to function because of resistance of the leukemia to the drug and radiation treatment."

Recent findings from several centers indicate that HLA-identical bone marrow transplantation results in cure of approximately 50 per cent of individuals with severe aplastic anemia, and prolonged remissions or cure of 10 to 15 per cent of individuals with advanced acute leukemia. These findings represent a considerable achievement since both diseases are almost uniformly fatal with any other treatment now available.

Monroe underwent his first bone marrow extraction in May of 1977 and received the bone marrow back in July. "I had already been in total remission for more than

six months and had been able to cherish my wife, Lynn, for nearly nine," he says. "The doctors who first diagnosed me had tried to discourage marriage. Herzig, however, let us marry in the hospital during my induction therapy because it was a hopeful action of which he could approve without professional doubts. I was given my first transplant when I was still in remission. Herzig told me he would like to do that in most of his patients, but that relapses often occur unpredictably," Monroe says.

Herzig remarks that his preliminary experience with the technique has been encouraging. "We store bone marrow from individuals with acute leukemia during a period of remission. When relapse of their disease occurs, we treat them with cyclophosphamide and total body irradiation, followed by transplantation with



Bone marrow aspiration needles are inserted into the iliac crest (below) to withdraw bone marrow cells. The syringes are then emptied into a beaker.

the bone marrow which has been stored frozen," he says. Herzig's technique eliminates the risk of graft versus host disease because the individual's own stored bone marrow is an identical, compatible match with their immune system.

It is not known for how long human bone marrow can be stored in the frozen state without loss of activity. To date, human bone marrow stored for up to 23 months has been used. In experiments with dogs at the National Cancer Institute it has been found that bone marrow can be stored for as long as three years without appreciable loss of ability to restore function.



“The most serious potential problem with this approach,” Herzig says, “is the possibility that some

leukemic cells remain hidden in the frozen bone marrow, and will be returned to the individual with the transplanted bone marrow."

Prior to autotransplantation, the recipient receives treatment with drugs or radiation or a combination of the two. The therapy kills the leukemic cells.

The bone marrow is infused between 36 and 48 hours after the last cyclophosphamide treatment to allow the body time to eliminate the drug so that it will not interfere with the transplanted bone marrow. "The transfusion of bone marrow takes just a few minutes," Herzig explains. "What takes the time is for the stem cells to divide and fill the bone marrow cavity," he says. The entire process of recovery takes from two to four weeks. Bone marrow is a self-sustaining organ, so if enough of the stem cells, the primitive cells, are transplanted, it can be completely regenerated by taking a small portion of the normal bone marrow and transplanting it.

During the two to four week period required for the new bone marrow to take, the recipient is at risk of infection due to low white blood cell counts and bleeding due to low platelet counts. Isolation techniques and white blood cell transfusions may be used to decrease the risk and severity of infections, and platelet transfusions are given to prevent bleeding.

Monroe's first transplant, which was performed using high doses of drugs without radiation, extended his remission without interruption to April of 1978. During that time Herzig and his team were able to store his bone marrow a second time. Monroe did relapse, but with a second transplant, after preparation with cyclophosphamide and total body irradiation, complete re-



mission was again attained and he remains in good health as of his most recent blood check.

Monroe has adopted a feeling of resignation about his disease. "I was really optimistic about a clinical cure after my first transplant," he says. "The relapse made me feel vulnerable again, but there is still that 10 to 15 per cent cure rate that Herzig has helped to build. The universe is so large—I'm sometimes unhappy, but my situation is not unique. I may be angry when I read about industries that are still lax about putting controls on carcinogens, but it is hard to direct anger over leukemia at any one thing or person because no one knows the exact cause.

"I get my strength from the belief that 51 per cent of everyone's personality is good rather than bad, and that humanistic ideals still exist for a continued struggle to perfect the human condition. I have difficulty envisioning an after life, so I am just hopeful that my clinical record will help Herzig and others like him spare someone else down the road," Monroe says.

Of the first eleven autograft recipients (six acute leukemia and five lymphoma) treated with cyclophosphamide and total body irradiation, four are in remission for four to eleven months after transplantation. Four individuals with leukemia have relapsed at three

Geoffrey Herzig, M.D., assistant professor of medicine, stores bone marrow cells in plastic bags in a liquid nitrogen freezer.

to six months and three individuals with lymphoma failed to achieve complete remission. "All of the recipients have recovered bone marrow function," Herzig says, "which indicates that the freezing procedure is effective in preserving the bone marrow stem cells." With characteristic caution, Herzig says, "while these initial results are promising, in order to fully evaluate this approach, a larger number of individuals will have to be observed for longer periods of time."

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